

# Estrogenic Side Effects of Androgen Deprivation Therapy

Theresa A. Guise, MD,\* Michael G. Oefelein, MD, FACS,<sup>†</sup>  
James A. Eastham, MD,<sup>‡</sup> Michael S. Cookson, MD,<sup>§</sup>  
Celestia S. Higano, MD,<sup>||</sup> Matthew Raymond Smith, MD, PhD<sup>¶</sup>

\*Department of Internal Medicine, University of Virginia, Charlottesville, VA; <sup>†</sup>Northwest Urology Clinic, Mount Vernon, WA; <sup>‡</sup>Division of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY; <sup>§</sup>Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN; <sup>||</sup>Departments of Medicine and Urology, University of Washington, Seattle, WA; <sup>¶</sup>Genitourinary Unit of Oncology, Massachusetts General Hospital, Boston, MA

*Androgen deprivation therapy (ADT) is part of standard therapy for locally advanced or metastatic prostate cancer and is frequently used in men with a rising prostate-specific antigen following radical prostatectomy or radiation therapy. In some men, ADT may be administered for years or even decades. The intended therapeutic effect of ADT is testosterone deficiency. Because estrogen is a normal metabolite of testosterone, ADT also results in estrogen deficiency. ADT has a variety of adverse effects, many of which are primarily related to estrogen deficiency. Bone mineral density may decrease by 4% to 13% per year in men receiving ADT. The fracture rate for patients on ADT averages 5% to 8% per year of therapy. Hot flashes, gynecomastia, and breast tenderness are common side effects associated with ADT. In the clinic, minimum baseline testing should include weight measurement, blood pressure reading, and fasting lipid panel and serum glucose tests. Currently, there are no large outcome trials in men on ADT testing the available therapies for adverse effects. No therapies are specifically approved for treatment of adverse effects in men on ADT. Although some therapies can be used for a single indication (based upon small studies), there is currently no agent to treat the multiple estrogenic side effects of ADT.*

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**P**rostate cancer is one of the most commonly diagnosed malignancies in men worldwide. In the United States, prostate cancer incidence increased steadily throughout the second half of the 20th century. This increase appears to be related to the rise in life expectancy and the associated increase in the number of older men at risk for prostate cancer. Other factors, including the widespread use of prostate-specific antigen (PSA) screening, have also contributed to the increase

in prostate cancer incidence in the past 2 decades. PSA screening identifies a large number of men with asymptomatic prostate cancer. The annual incidence of prostate cancer peaked at 350,000 cases in 1993. After declining in the late 1990s, the annual incidence of prostate cancer is rising again.

In contrast to the marked variations in the annual rates of prostate cancer diagnosis, prostate cancer mortality rates have declined steadily since 1990. Earlier diagnosis and treatment have contributed to the decline in cancer-specific mortality. The American Cancer Society estimates that the current 5-year relative survival for men with prostate cancer is nearly 100%, up from 76% in 1984 to 1986.<sup>1</sup> For most men, prostate cancer is now a chronic disease.

The improvements in prostate cancer outcomes, however, have been accompanied by a greater burden of treatment for prostate cancer survivors. Approximately one-third of the estimated 2 million prostate cancer survivors, for example, currently receive treatment with a gonadotropin-releasing hormone (GnRH) agonist.<sup>2</sup> Loss of sexual interest, vasomotor flushing, and fatigue have long been recognized as adverse effects of GnRH agonists and other forms of androgen deprivation therapy (ADT), including bilateral orchiectomies. Clinical research over the past decade has demonstrated a broader array of clinically important adverse effects of ADT, including osteoporosis, obesity, diabetes, and cardiovascular disease.

This article will review the current issues related to common adverse effects of ADT, including osteoporosis, vasomotor flushing, gynecomastia, and cardiovascular disease. This state-of-the-art information will help provide urologists and other clinicians with an understanding of the scope of the clinical problems, the

mechanisms responsible for these adverse effects, and emerging strategies to prevent treatment-related morbidity for prostate cancer survivors.

### Osteoporosis

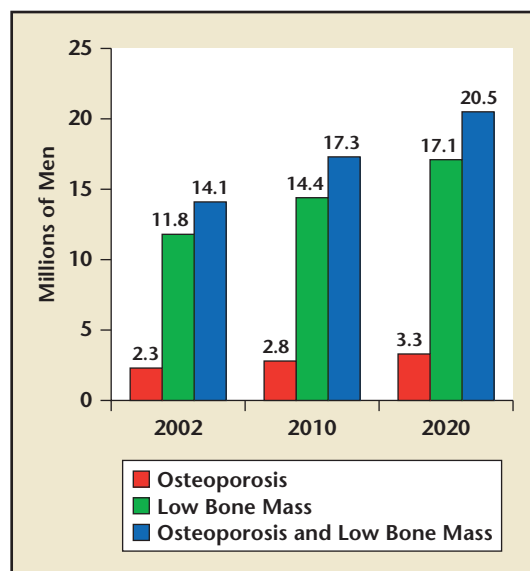
Osteoporosis is a skeletal disorder characterized by compromised bone strength that raises a person's risk of fracture.<sup>3</sup> Contrary to popular belief, osteoporosis is not only a woman's disease. More than 2 million American men have been diagnosed with osteoporosis, a number predicted to exceed 3 million (a 33% increase) by the year 2020 (Figure 1).<sup>4</sup> After age 50, men lose an average of 0.5% of their bone mineral density (BMD) each year.<sup>5</sup> (In comparison, women lose 1% and 2% of their BMD each year in late and early menopause, respectively.)<sup>5</sup> One in 4 men older than 50 is likely to experience a fracture at some point during his lifetime, and men who experience hip fractures are more likely to die than women who do.<sup>6,7</sup>

Given the lack of a menopause-equivalent event in men, it is important to explore the mechanisms by which men develop osteoporosis.

Male hypogonadism, in general, and ADT, in particular, represent important risk factors. In some men with prostate cancer, a medically induced hypogonadal (menopausal) state is created. This hypogonadal state adversely affects bone health by reducing the substrate (eg, androgens) for bone aromatase conversion to estrogens. The ensuing hypoestrogenic state has a greater consequence on BMD than the hypoandrogenic state induced by castration therapy.<sup>8,9</sup> Despite its efficacy, ADT has significant side effects. One of the most serious is the propensity to accelerate BMD loss and to bring about the development of osteoporosis.<sup>10</sup> BMD may decrease by 4% to 13% per year in men receiving ADT, resulting in an exponential increase in fracture risk.<sup>11-13</sup> The trend toward early administration of ADT combined with the ensuing protracted clinical course for prostate cancer patients frequently results in men who receive this therapy for years or even decades.<sup>14</sup> The clinical consequences of accelerated BMD loss affect both the quality and quantity of life.

We will begin our discussion of osteoporosis in men with an exploration

Figure 1. Prevalence of Osteoporosis and Low Bone Mass in Men Aged 50 and Over. Adapted with permission from America's Bone Health: The State of Osteoporosis and Low Bone Mass in Our Nation, page 5, 2002, National Osteoporosis Foundation, Washington, DC 20037.<sup>4</sup>



of the clinical consequences. We will then describe evaluation and diagnosis, including the role of dual-energy x-ray absorptiometry (DXA) and risk factors particular to men. Our discussion of osteoporosis will conclude with an examination of treatment considerations for bone loss induced by ADT therapy.

### Clinical Consequences

It has been estimated that osteoporosis accounts for greater loss of disability-adjusted life-years than almost all types of cancer.<sup>6</sup> The consequences of male osteoporosis are many. The loss of BMD correlates with an exponentially increased risk of fragility fractures.<sup>15</sup> Fragility fractures are an indicator of osteoporosis and, once identified, require a formal assessment of BMD with a DXA scan and the institution of behavioral and medical therapies targeting osteoporosis. Although lower BMD correlates with an increasing risk of fracture, in some cases, structurally weak bone can appear dense on DXA scans. Examples include poorly woven dense bone (eg, osteoblastic lesions) and bones affected by osteopetrosis (in which bisphosphonates can freeze normal bone turnover). Therefore, the assessment of bone strength must be multifactorial and, ultimately, fracture outcomes most accurately assess bone strength. Fractures of the spine, wrist, and hip have important and varying impacts on quality and quantity of life. Although vertebral fractures are subclinical in 2 out of 3 cases, they are associated with up to a 50% likelihood of another fracture within 1 year as well as excess mortality as high as 20%.<sup>16</sup>

In men, osteoporotic fractures most often occur in the vertebrae or hip and less commonly in the radius.<sup>17</sup> Most fractures occur almost a decade later in men as compared with women.<sup>17</sup> In men, hip BMD is strongly

associated with the risk of nonvertebral fracture and hip fracture.<sup>18</sup> Hip fractures represent the most serious consequence of osteoporosis. Fewer than half of hospitalized hip fracture patients recover their pre-fracture competence in activities and, at 6 months after the injury, only 15% of patients can walk without assistance. After a hip fracture, an estimated 10% to 24% excess death rate has been reported, with higher mortality in men (31%) as compared with women (17%).<sup>7</sup> In addition to these important clinical consequences, hip fractures generate an economic burden that averages more than US\$81,000 per patient.<sup>19</sup>

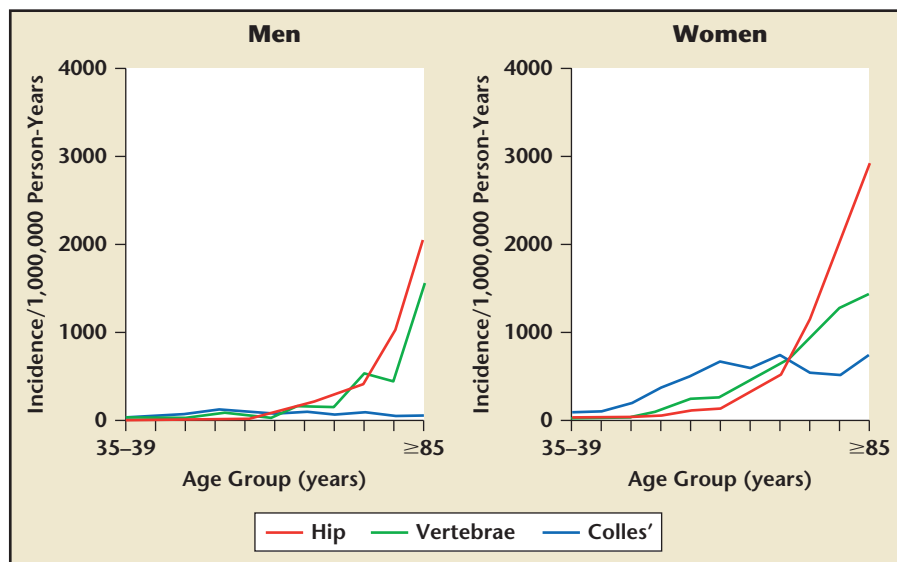
Taken together, these data highlight the connection between declining bone health and clinical consequences—namely, deterioration in quality of life, excess mortality, and a large economic cost to patients and society. The incidence of fracture as a function of age, gender, and site of injury is shown in Figure 2. It is important to note that the exponential increase in fractures as the population

ages correlates with the loss of sex steroids and the consequential loss of BMD.

Population-based fracture rates are generally lower for men than women. One presumed factor is differences between the sexes in bone size. The skeleton is an architectural structure whose chief role is mechanical support. The ability of bones to withstand pressure sustained on impact and thus avoid fracture is generally thought to rise with increasing diameter and thickness. This notion has, however, been challenged as studies using advanced imaging techniques have suggested that sex differences in fracture rates are due to differences in patterns of bone loss during aging.<sup>20</sup>

Despite lower fracture rates overall, the absolute risk of fracture appears to be similar in men and women of the same age and with the same areal BMD as measured by DXA. Similarly, the risk of fracture increases substantially as BMD decreases. In elderly men, the hazard ratio for a hip fracture is 2.3 for each standard deviation decrease in femoral neck BMD.<sup>21</sup>

Figure 2. Fracture risk as a function of age and gender. Reprinted with permission from Cooper C and Melton LJ III.<sup>115</sup>



Estrogen has been identified as a key determinant of skeletal bone health in men. Patients with congenital aromatase deficiency and estrogen-receptor mutations have low BMD without suppression of circulating levels of androgens.<sup>22,23</sup> In addition, medical castration by use of estrogen in men with prostate cancer does not appear to decrease BMD.<sup>24</sup> Circulating estradiol concentrations have been positively associated with increased BMD in older men, but such measurements are not routinely performed as part of the evaluation for osteoporosis in men.<sup>24</sup>

#### Evaluation and Diagnosis

DXA is often used to measure BMD for diagnosis (Table 1), but density can also be determined by techniques such as quantitative computed tomography (QCT). The threshold values for diagnosis should not necessarily be seen as thresholds for therapeutic intervention because BMD is not the sole factor to influence bone strength or fracture risk. An individual who has sustained a fragility fracture (low-trauma fracture at typical sites such as the vertebrae, hip, or radius) can be diagnosed with osteoporosis regardless of his or

her BMD. The World Health Organization (WHO) criteria were developed for postmenopausal women but have been routinely applied to men using gender- and race-specific reference databases.<sup>3</sup> Although there is controversy regarding this approach, BMD has continued to be a strong predictor of fracture risk in older men, as it is in women.<sup>18</sup>

The first step in assessing fracture risk is a thorough assessment of clinical risk factors, through which one can identify a subgroup of patients for whom the risk of a future fracture is high enough to warrant therapy, regardless of baseline BMD. A large population-based observational trial in the United States involving 5995 men aged 65 years and older identified the following risk factors for nonspine fracture: decreased total hip BMD, any fractures after age 50 years, fall history, gait instability, and depressed mood with use of tricyclic antidepressants.<sup>25</sup> Total testosterone or estradiol levels were also associated with reduced BMD.<sup>26</sup> Osteoporotic fractures can occur from falls, and the fall risk has been shown to be raised in men with low bioavailable testosterone levels, independent of poor physical functioning.<sup>27</sup>

Men might be at higher risk than women of developing osteoporosis from secondary causes of low BMD. The most commonly identifiable risk factors for male osteoporosis are summarized in Table 2.<sup>6,28,29</sup> Factors include glucocorticoid steroid treatment, hypogonadism, slender body mass index ( $\leq 25 \text{ kg/m}^2$ ), and white race.<sup>30</sup> Additionally, the gradual development of idiopathic androgen decline in aging men has become an increasingly recognized entity.<sup>31</sup> This hypogonadal state represents an important risk factor for male osteoporosis. Modification of these and

**Table 1**  
Defining Osteoporosis by BMD Based on the WHO Criteria

Category	Definition by BMD
Normal	BMD is within 1 SD from a young normal adult (T-score greater than or equal to $-1.0$ )
Osteopenia	BMD is between 1 and 2.5 SD below a young normal adult (T-score between $-1$ and $-2.5$ )
Osteoporosis	BMD is 2.5 SD or more below that of a young normal adult (T-score at or below $-2.5$ )
Severe osteoporosis (established)	BMD more than 2.5 SD below a young adult mean in the presence of one or more fragility fractures

BMD, bone mineral density; WHO, World Health Organization; SD, standard deviation. Adapted from the World Health Organization.<sup>109</sup>

**Table 2**  
Risk Factors for Osteoporosis in Men

Prolonged exposure to certain medications
Steroids*
Anticonvulsants
Certain cancer treatments
Aluminum-containing antacids
Low levels of testosterone*
Prostate cancer
Lifestyle habits
Smoking*
Excessive alcohol use*
Low calcium intake
Inadequate physical exercise
Age
Family history
White race
Personal history of fracture as an adult
History of fractures in a first-degree relative
Recent falls
Impaired vision despite correction
Dementia
Poor health/frailty

\*Major risk factor.

Data from the National Osteoporosis Foundation<sup>38</sup> and Orwoll ES and Klein RF.<sup>28</sup>

other risk factors thus remains an important goal in preventing and treating osteoporosis.

In patients with risk factors, BMD may be utilized to monitor response to therapy. On the other hand, individuals with a paucity of risk factors may not warrant BMD testing because their fracture risk is low regardless of bone density measurements. Thus, the National Osteoporosis Foundation has provided a set of guidelines to aid practitioners in identifying patients for whom BMD testing is appropriate.<sup>32</sup> These and similar guidelines issued by Medicare and the International Society for Clinical Densitometry are not all-encompassing and, therefore, should be used in the context of a patient's particular situation.

BMD testing remains a cornerstone of osteoporosis diagnosis and assessment of response to treatment. Central DXA is the standard for BMD testing. Central DXA has been used extensively in epidemiologic studies and, therefore, its relationship to fracture risk has been best characterized. Fracture prediction at a specific site is most accurate for BMD measurements at that particular site, although a general fracture risk assessment can be estimated from measurement at any site.

QCT of the spine is another central modality for bone density measurement. The greatest advantage of this technology is that it provides a true volumetric assessment of bone density, whereas DXA only provides an areal density. QCT requires specific software, and it has not been traditionally used in epidemiologic studies or longitudinal studies of treatment effect. Furthermore, QCT results in a high radiation exposure far in excess of that observed with DXA. This technology may best be used in patients at the extremes of size or weight.

Peripheral technologies such as pQCT, pDEXA, and quantitative ultrasound are increasingly being used for

screening purposes. The WHO criteria should not be applied to these measurements, and thus it is recommended that a patient with a positive study undergo central DXA measurement. Furthermore, sites traditionally measured by these methods respond poorly to osteoporosis treatment, and it is recommended that central sites be used to assess response to therapy. However, peripheral BMD does provide an assessment of global fracture risk, as was recently demonstrated in 2 large prospective studies, and may serve as a cost-effective initial screening tool.

Although osteoporosis has few diagnostic signs that can be discerned in a physical examination, there are a number of findings that can alert the practitioner to the possibility of disease and/or an increased fracture risk. Poor visual acuity and depth perception, decreased proprioception, decreased proximal muscle strength, and an impaired "get up and go test" are all risk factors for fall and fracture and can be easily assessed in the clinic. Furthermore, kyphotic deformities of the spine are late sequelae of vertebral fractures and should prompt the physician to pursue further diagnosis and treatment.

All patients diagnosed with osteoporosis should undergo basic laboratory testing for secondary causes of osteoporosis. This recommendation is especially important for men, in whom secondary causes for osteoporosis are more common than in women (Table 3).<sup>28</sup> These tests should include, at a minimum, measurement of calcium, phosphorus, magnesium, creatinine, parathyroid hormone, and 25(OH) vitamin D levels. The prevalence of vitamin D deficiency in the elderly population is estimated to be between 25% and 54%. This number is probably even higher for institutionalized or debilitated individuals. Vitamin D deficiency may, in turn, lead to

secondary hyperparathyroidism and its associated adverse effects on bone. Thus, vitamin D deficiency should be routinely screened for and aggressively treated. In the absence of prostate cancer, all men should have a serum testosterone measurement because treatment of hypogonadism may result in increased bone mass. In addition, other tests such as serum and urine protein electrophoresis and screening tests for hypercortisolism or malabsorptive syndromes should be obtained in selected patients. Finally, whether to measure 24-hour urine excretion for calcium is controversial. Idiopathic hypercalciuria has been associated with secondary hyperparathyroidism and low BMD. Such patients may benefit from treatment with thiazide diuretics to reduce renal calcium excretion.

#### Osteoporosis and ADT

ADT is standard treatment for men with locally advanced or metastatic

**Table 3**  
**Secondary Causes of**  
**Osteoporosis in Men**

Hypogonadism
Glucocorticoids
Alcoholism
Gastrointestinal disorders
Hypercalciuria
Smoking
Anticonvulsants
Neoplastic diseases
Rheumatoid arthritis
Thyrotoxicosis
Immobilization
Osteogenesis imperfecta
Homocystinuria
Systemic mastocytosis

Data from Orwoll ES and Klein RF.<sup>28</sup>

prostate cancer and is frequently used in patients with a rising prostate-specific antigen (PSA) following radical prostatectomy or radiation therapy (RT). ADT consists of treatment with a GnRH agonist, combined androgen blockade (GnRH analog plus antiandrogen), or, less commonly, bilateral orchiectomy. ADT is a highly effective therapy that prolongs life in patients with lymph node positive prostate cancer<sup>33</sup> and intermediate and high-risk clinically localized disease.<sup>34-36</sup> The chronic (> 10 years) administration of ADT has become an increasingly common clinical reality.<sup>14</sup> Unfortunately, the impact of ADT on estrogens and androgens that modulate bone remodeling often results in rapid and significant loss of BMD.

As mentioned previously, BMD may decrease by 4% to 13% per year in men receiving ADT, resulting in an exponential increase in fracture risk.<sup>11-13</sup> As one would expect given this BMD loss, a corresponding increase in the rate of fragility fractures has been reported (Table 4). The fracture rate for patients on ADT averages 5% to 8% per year of therapy. Several independent investigators have confirmed that prostate cancer

patients treated with androgen suppression are at risk for skeletal fractures,<sup>29,30</sup> and this risk increases with the duration of therapy.<sup>29</sup> Slender, white men are at greatest risk for skeletal fractures.<sup>30</sup> Conversely, African American men and men with body mass indexes exceeding normal (> 25 kg/m<sup>2</sup>) are at less risk, even with prolonged duration (> 10 years) of androgen suppression.<sup>30</sup> Morote and associates<sup>37</sup> have reported the longitudinal assessment of BMD with standard DXA in men treated with ADT. These authors have reported that 20% of prostate cancer patients have osteoporosis before ADT is initiated. This proportion increases with each year of therapy. More than 90% of men on ADT have osteoporosis after 10 years of therapy. This important observation highlights the relationship between prostate cancer, hypogonadism, and bone health. For prostate cancer patients treated with ADT who experienced a fracture, Oefelein and associates<sup>30</sup> have reported a significantly reduced overall survival. This multivariate analysis adjusted for competing causes of death and established risk factors for survival (stage, grade, etc). Furthermore,

it should be noted that within this cohort, the median duration of ADT exceeded 10 years.

The decrease in BMD is compounded by the fact that many men with prostate cancer are osteopenic or osteoporotic before they start taking ADT. Men with prostate cancer may also have other risk factors for developing osteoporosis (Table 2).<sup>28,38</sup> Consequently, screening, prevention, and treatment of bone loss are critical for patients receiving ADT for prostate cancer.

**Diagnostic and treatment considerations.** Early diagnosis of bone loss and prompt initiation of preventive and pharmacologic measures to delay or prevent decreased BMD are essential in men with advanced prostate cancer who are initiating ADT. Although no consensus exists on the use and frequency of BMD testing for prostate cancer, a recent literature review provided recommendations for screening. Diamond and colleagues<sup>12</sup> proposed measuring BMD in patients considered to be at high risk for osteoporosis. They suggested that all men at increased risk for fracture (those receiving ADT and/or with a history of fracture) undergo BMD assessment with DXA. The frequency of follow-up BMD testing depends on the resulting T-score (Figure 3). Patients with a T-score of -1 to -2.5 (the level for osteopenia or osteoporosis) should have follow-up DXA scans after 6 to 12 months; those with a T-score at or greater than -1 should be rescreened every 2 years.

**Lifestyle changes.** Lifestyle interventions can have a major impact on bone health and may delay the onset and severity of ADT-associated bone loss. A regular exercise program can decrease bone loss, increase bone and muscle strength, and improve stability, thus reducing fracture risk.<sup>39</sup> Exercise should include a combination of weight-bearing aerobic exercise

**Table 4**  
**Fracture Prevalence in Men Treated With ADT**

Study	N	Duration of ADT	Fracture Prevalence
Smith MR et al <sup>110</sup>	3779	1 year	7.9%
Townsend MF et al <sup>111</sup>	224	22 months	9%
Hatano T et al <sup>112</sup>	218	28 months	6%
Oefelein MG et al <sup>30</sup>	181	47 months	13%
Daniell HW <sup>10</sup>	59	< 48 months	14%
Shahinian VB et al <sup>29</sup>	14,394	4 years	20%
Krupski TL et al <sup>113</sup>	716	> 697 days over 7 years	45%
Melton LJ et al <sup>114</sup>	429	15 years	73%

ADT, androgen deprivation therapy.

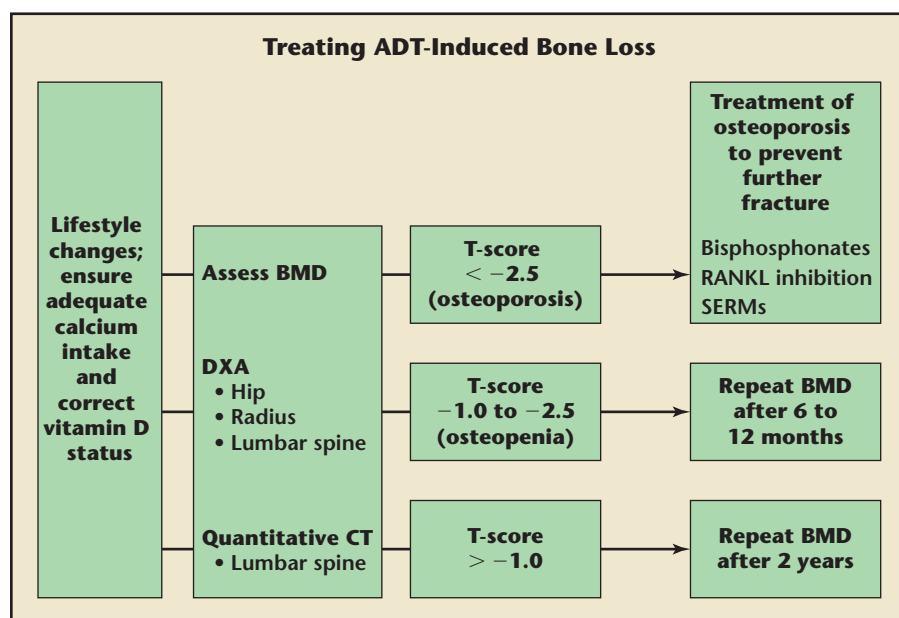


Figure 3. Clinical algorithm for assessment and treatment of ADT-associated bone loss in men with prostate cancer. BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; RANKL, receptor activator of the nuclear factor kappa  $\beta$  ligand; SERMs, selective estrogen receptor modulators; CT, computed tomography. Reprinted with permission from Diamond TH et al.<sup>12</sup>

and strength training, performed for 30 min/d 2 to 4 times a week.<sup>40</sup> Other lifestyle changes that serve to promote bone health involve avoidance of excessive alcohol and caffeine, as well as smoking cessation.<sup>41</sup>

Nutritional intervention is a simple way to ensure adequate levels of the nutrients needed to maintain bone formation, especially calcium and vitamin D. Dietary sources of calcium include dairy products, green leafy vegetables, and nuts. Sunlight and food such as fortified milk and liver provide vitamin D. Men with prostate cancer who are initiating ADT should take daily supplements to obtain sufficient calcium and vitamin D. Calcium intake (dietary and supplemental) should be 1200 mg/d. The supplements should be taken in divided oral doses. Doses of vitamin D should range from 400 to 800 IU/d. Newer data suggest that more vitamin D may be necessary to reduce the risk of fracture in older individuals ( $\geq 60$  years).<sup>42</sup> Supplementation to achieve 800 IU/d of vitamin D should be con-

sidered for older men with prostate cancer.

### Systemic Therapy

**Bisphosphonates.** Bisphosphonates are nonhydrolyzable pyrophosphate analogs that have shown significant clinical activity in preventing the bone loss and high bone turnover seen in patients with prostate cancer and other diseases. Bisphosphonates bind to bone surfaces at sites of active remodeling and are internalized by osteoclasts, which inhibits the activity of these bone-degrading cells.

Both oral and intravenous (IV) bisphosphonates are available for treatment of ADT-induced bone loss. There is good evidence that bisphosphonates improve BMD in men on ADT. However, they are not specifically approved by the Food and Drug Administration for the treatment of bone loss in men with hormone-sensitive prostate cancer, and there is no evidence they reduce fractures in this population. Oral formulations are limited by poor absorption, which

requires large doses that can induce gastrointestinal (GI) toxicities. Strict adherence to administration guidelines is necessary to improve absorption and reduce toxicity. Patients should be advised to take oral bisphosphonates on an empty stomach to improve absorption, and to remain upright for 30 minutes to reduce the occurrence of GI adverse effects. IV bisphosphonates are usually well tolerated and are not limited by GI pharmacodynamic issues. Approximately 20% of patients treated with IV bisphosphonates develop flu-like symptoms, including arthralgia, myalgia, nausea, low-grade fever, and increased bone pain.<sup>43</sup> These symptoms typically occur after the first dose and generally are self-limiting. Acute renal toxicity can occur following rapid IV administration of bisphosphonates.<sup>44</sup> Patients on long-term therapy may have increases in serum creatinine levels. Serum creatinine should be monitored in patients on bisphosphonates, and the dosage adjusted based on creatinine clearance. IV bisphosphonates are contraindicated in patients with severe renal impairment (creatinine clearance  $< 30$  mL/min).

Osteonecrosis of the jaw (ONJ) has emerged as an important adverse effect of bisphosphonates—particularly for cancer patients receiving frequent IV pamidronate or zoledronic acid for bone metastases. Among 1203 survey respondents with myeloma or breast cancer who were treated with bisphosphonates, at 3 years ONJ was reported in 10% of patients who received zoledronic acid and in 4% of patients treated with pamidronate.<sup>44</sup> The incidence increased with duration of therapy and was similar for both tumor types. A different retrospective review of 943 patients with metastatic breast cancer who received these bisphosphonates found a much lower incidence of 0.6%.<sup>45</sup> Risk factors include prior or

concomitant chemotherapy, radiotherapy or steroid therapy, trauma, infection, and dental problems (past or present).<sup>46</sup> Physicians should, therefore, ensure that a thorough oral examination is conducted at the start of bisphosphonate therapy, with removal of all dental infections prior to initiation of treatment. Physicians should counsel patients regarding the importance of good oral hygiene. Dental procedures and major debridement surgeries should be avoided if possible. Effective treatment of this avascular necrosis has not been determined, although conservative management with penicillin-type antibiotics and chlorhexidine rinses seems effective.<sup>46</sup> Interruptions in bisphosphonate therapy could be prudent among patients who develop ONJ. Although a causal effect of bisphosphonate therapy has not yet been established, increased awareness of the risk of this adverse event will help reduce morbidity in patients receiving such therapy.

IV bisphosphonates have been evaluated similarly for prevention of bone loss in prostate cancer and were found to be more potent than oral forms.<sup>47-49</sup> In a randomized study of 41 men with locally advanced, node-positive, or recurrent prostate cancer but with no metastases, pamidronate prevented bone loss in the spine and hip but failed to increase BMD significantly above baseline.<sup>50</sup> In contrast, zoledronic acid not only prevented loss of BMD but also increased BMD over baseline values.<sup>51</sup> This trial randomized 106 men with nonmetastatic prostate cancer who were beginning ADT to receive zoledronic acid (4 mg every 3 months for 1 year) or placebo. Significant increases in BMD ( $P < .001$ ) occurred in the lumbar spine, femoral neck, trochanter, and hip with zoledronic acid compared with placebo (Figure 4).

**RANKL inhibition.** Signaling through the receptor activator of the

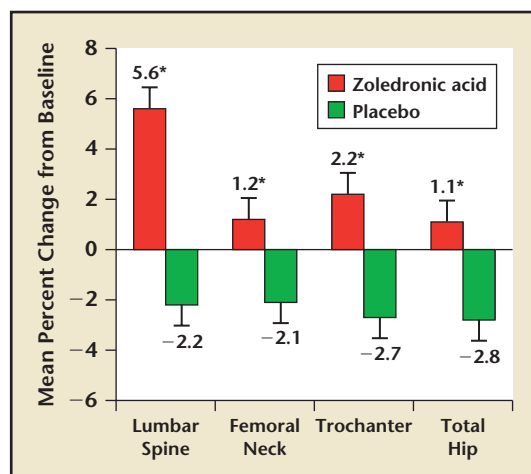
nuclear factor kappa  $\beta$  ligand (RANKL) plays an important role in the differentiation and activation of osteoclasts. This process is involved in bone loss in several diseases, including osteoporosis and prostate cancer.<sup>52,53</sup> Inhibition of RANKL binding to the receptor activator of the nuclear factor kappa  $\beta$  receptor inhibits the activity of osteoclasts and decreases bone turnover. Therapeutic targeting of RANKL by means of a human monoclonal antibody (Denosumab®; Amgen; Thousand Oaks, CA), a natural soluble RANKL receptor, may therefore retard bone loss. In a dose-escalation study, a single administration of this agent in postmenopausal women resulted in a rapid, dose-dependent and sustained decrease in bone turnover.<sup>54</sup> A randomized, placebo-controlled phase III trial of this agent has been initiated in 1400 men receiving a luteinizing hormone-releasing hormone (LHRH) agonist for prostate cancer (subcutaneous Denosumab every 6 months) to prevent vertebral fractures and decline in BMD. No interim data are available for this trial.

**Selective estrogen-receptor modulators.** Although estrogen is principally considered a female reproductive hormone, it is bioactive in multiple male tissues, including bone.

Estrogens have functional receptors in both osteoblasts and osteoclasts and appear to be the dominant sex hormone in regulating the male skeleton. Estrogens control osteoclastic activity, and estrogen deficiency induces bone loss. Selective estrogen-receptor modulators (SERMs) bind to the estrogen receptor and have been demonstrated to reduce bone loss. Raloxifene is a SERM that is approved to prevent and treat osteoporosis in women. In a 12-month open-label study, 48 men with nonmetastatic prostate cancer receiving a GnRH agonist were randomly assigned to raloxifene (60 mg/d) or no raloxifene.<sup>55</sup> Raloxifene decreased biochemical markers of bone turnover and significantly increased BMD of the hip.

Toremifene is a SERM that is approved for the treatment of advanced breast cancer and is also being evaluated for the treatment of osteoporosis and other complications associated with hormonal therapy for prostate cancer. In a 6-month, placebo-controlled study, 46 men with prostate cancer who were receiving a GnRH agonist were randomly assigned to receive either toremifene or a placebo.<sup>56</sup> In men receiving toremifene (60 mg/d), BMD significantly increased as compared with

Figure 4. Zoledronic acid increases bone mineral density in patients with non-metastatic and metastatic prostate cancer on ADT. \*Statistically significant difference for zoledronic acid compared with placebo ( $P < .001$ ). Reprinted with permission from Smith MR et al.<sup>51</sup> Copyright © Elsevier 2003.



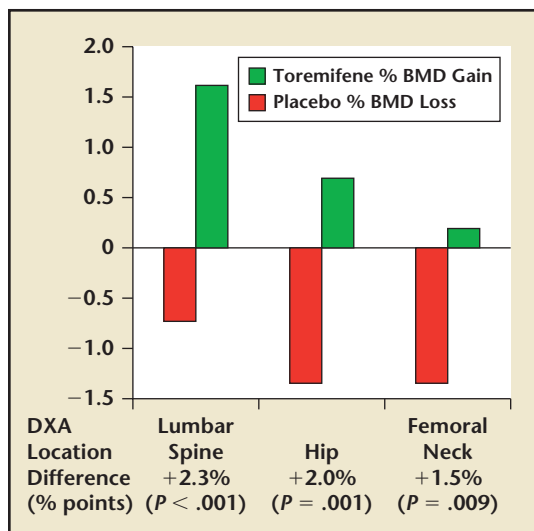


Figure 5. Toremifene 80 mg increased BMD in prostate cancer patients treated with androgen deprivation therapy. Interim analysis of first 197 patients. BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry. Adapted with permission from Smith MR et al.<sup>116</sup>

men receiving placebo. In an ongoing phase 3 study, 1392 men who are receiving a GnRH agonist for prostate cancer were randomly assigned to either toremifene (80 mg/d) or placebo. The primary endpoint is vertebral fractures at 24 months. Secondary endpoints include BMD, hot flashes, gynecomastia, and lipid changes. An interim analysis after 12 months demonstrated a significant improvement in BMD in those receiving toremifene<sup>56</sup> (Figure 5).

### Summary

Recent progress in the early screening and treatment of patients with prostate cancer has led to the identification of greater numbers of men who are eligible for therapy and who are surviving longer. This development has expanded the number of older patients who are being treated with ADT or who are eligible for treatment. Additionally, the natural history of this disease causes significant bone loss in many patients before treatment is initiated. The loss of bone density seen with ADT requires clinicians to be aware of the scope of this growing problem and its treatment. Regular screening of patients at

risk of bone loss is needed for early detection and treatment. Lifestyle changes are recommended for all men receiving long-term ADT. Ongoing randomized controlled trials will assess the efficacy of toremifene and denosumab for prevention of fractures during ADT.

### Hot Flashes and Gynecomastia

Hot flashes, gynecomastia, and breast tenderness are common bothersome side effects associated with ADT. Surprisingly, these distressing symptoms have received little attention thus far. Few clinical trials have been conducted to assess the available treatment options.

#### Hot Flashes

In men with prostate cancer, hot flashes are induced by ADT, either from surgical castration in the form of bilateral orchiectomy or medical castration in the form of hormone treatment. For women, hot flashes occur at menopause and are a natural consequence of decreasing sex hormone levels. Hot flashes in men being treated with ADT are the result of a sudden and often dramatic change in the hormonal milieu.<sup>57</sup> In menopausal

women, vasomotor symptoms often disappear after 2 to 5 years, but may persist for 10 to 15 years. For men on ADT, however, hot flashes tend not to disappear. Instead they usually persist with the same frequency and duration throughout therapy.<sup>58</sup> In 50% of patients, hot flashes have been reported beyond 5 years. Thus, in men treated with castration, symptoms appear to be more severe and less prone to resolution than they are in postmenopausal women.

Hot flashes are among the most common distressing side effects of ADT. The incidence ranges from 50% to 80% among patients treated with orchiectomy, and 77% in patients treated with LHRH agonists.<sup>59,60</sup> Furthermore, up to one-third of men consider these symptoms to be the most distressing and warranting of treatment.<sup>61</sup> Cabot, in 1896, first described the effects of castration on benign prostatic hyperplasia as “. . . uncomfortable flushes of heat, similar to those experienced in women at the time of menopause.”<sup>62</sup> In 1941, Huggins and Hodges reported this side effect in 9 of 21 patients whose prostate cancer was treated by orchiectomy, with episodic hot flushes beginning 2 to 6 weeks postoperatively; it was described as “. . . profuse perspiration, often occurring at night, forcing the patient to throw off the bed covers.”<sup>63</sup> Clearly, these observations are astute and as applicable today as they were more than 60 years ago.

Hot flashes are generally defined as a sudden rush of warmth in the face, neck, upper chest, and back, which is sometimes associated with facial flushing, nausea, or both.<sup>60</sup> Symptoms include a perceived increase in temperature, reddening of the skin, and profuse sweating.<sup>64</sup> The duration of episodes may vary, lasting only seconds to as long as an hour. Hot flashes may be precipitated by heat, stress, changes in body position, or

ingestion of hot liquids, but most occur spontaneously without a definable inciting event.<sup>65</sup>

Although the exact etiology of hot flashes is debated, the underlying cause is thought to be an alteration in the feedback mechanism of the hypothalamus due to a decline in sex steroid hormones.<sup>61</sup> This alteration results in an increase in catecholamine secretion in response to a decrease in endogenous peptide secretion and stimulates the nearby thermoregulatory center (heat-losing mechanism). Stimulation of this thermoregulatory center leads to the perception of increased heat; previous imprinting by estrogen may play an additional role.<sup>66</sup>

There are currently no validated instruments or tools used to assess hot flashes. Several grading scales have been proposed that generally incorporate the duration and severity of symptoms into a simplified scoring system.<sup>60,67</sup> At a minimum, clinicians should attempt to assess the number of daily occurrences of hot flashes (1-3, mild; 4-9, moderate; and  $\geq 10$ , severe) and ask the patient whether the symptoms are bothersome enough to warrant therapy.

Most treatments used for hot flashes in men on ADT are similar to those recommended for postmenopausal women, among whom large-scale studies have been performed. The reported success of the available regimens varies widely and is dependent on study design, number of patients, duration of therapy, and method of assessing response to treatment. Additionally, the use of these therapies is tempered by the associated side effect profile as well as the availability of the intervention. A variety of treatments have been evaluated for men with bothersome hot flashes including estrogens (diethylstilbestrol [DES] and transdermal estrogen), progestins (megestrol acetate

and medroxyprogesterone acetate [MPA]), clonidine, and antidepressants, as well as alternative therapies such as soy or vitamin E supplementation and acupuncture.

**Estrogen therapy.** Estrogens appear to be efficacious in the treatment of hot flashes for men on ADT. Transdermal estrogens were evaluated in a pilot study of 12 men with prostate cancer who were being treated with ADT.<sup>68</sup> All patients had moderate-to-severe hot flashes. The 4-week trial compared treatment with low-dose (0.05 mg) and high-dose (0.1 mg) estrogen patches applied twice weekly. Overall, 83% of patients reported some improvement in symptoms. Moderate or major improvement was noted in 67% of patients using the high-dose patch and 25% of patients using the low-dose patch. In terms of side effects, mild, painless breast swelling or nipple tenderness was noted in 42% of patients using the high-dose patch and 17% of patients using the low-dose patch.

Another study in 14 men with prostate cancer assessed the use of DES for hot flashes following surgical castration.<sup>69</sup> Before treatment with the trial medication, all patients experienced 4 to 12 documented hot flashes daily. This crossover trial randomized patients to either 12 weeks of DES at 1 mg/d or placebo. Patients demonstrated a 100% response to DES, with 12 having complete resolution of their hot flashes and 2 experiencing a reduction in severity and frequency. Of the 14 patients receiving placebo, 3 reported a moderate reduction in frequency and severity and none reported complete resolution. Despite these success rates, enthusiasm for estrogens has been hampered by concern over side effects, which include gynecomastia, breast tenderness, cardiovascular morbidity, thromboembolic disorders, weight gain, and edema.<sup>65</sup>

**Progestins.** Progestins have also demonstrated proven efficacy in the treatment of hot flashes among men on ADT. One study of megestrol acetate (Megace®; Par Pharmaceutical Companies, Inc; Woodcliff Lake, NJ) included 66 men with prostate cancer on ADT.<sup>70</sup> Before treatment with megestrol acetate, all subjects had bothersome hot flashes with a median frequency of 8.4 per day. This double-blind, placebo-controlled, crossover trial evaluated megestrol acetate at a dose of 20 mg twice daily for 4 weeks, followed by placebo for 4 weeks, or vice versa. Hot flashes were reduced by 85% in the group receiving megestrol acetate compared with 21% in the placebo group ( $P < .001$ ). Frequency of hot flashes was decreased by at least 50% in 74% of patients in the megestrol acetate group as compared with 20% of patients in the placebo group. This study demonstrated that this progestin effectively reduces hot flashes in men on ADT. The fact that the placebo resulted in a 20% improvement in symptoms should be kept in mind during the assessment of data from pilot series that lack adequate control groups.

Another progestin that has been studied for the treatment of hot flashes is medroxyprogesterone acetate (MPA; Provera®; Pfizer; New York, NY). In a study of 48 men with prostate cancer being treated with ADT, 40 men received MPA at a dose of 400 mg intramuscularly and 8 received a dose of 150 mg intramuscularly.<sup>71</sup> The mean duration of symptoms prior to treatment was 8 months, and the mean duration of treatment was 43 months. With MPA, 91% of patients achieved symptomatic improvement, and 46% experienced a complete response. One patient in the MPA 150 mg dose group experienced a complete response. The median number of hot flashes decreased from 4 to 1 per day. Surprisingly, 27% of

patients needed only 1 to 2 injections for resolution of symptoms. In this study, there were no thromboembolic complications.

Side effects of progestational therapy with megestrol acetate include weight gain (increase in fat and loss of muscle), thromboembolic disorders, edema, lipid changes, and cardiovascular morbidity.<sup>70</sup> Perhaps more concerning is the possibility that this secondary hormonal manipulation may contribute to tumor growth and cancer progression.<sup>72</sup> Antiandrogen withdrawal syndrome, similar to that reported with more traditional peripheral antiandrogens, has also been reported in men on ADT after discontinuance of progesterone therapy.<sup>73</sup>

**Clonidine.** This alpha-2 receptor agonist inhibits the central release of catecholamines. Modest success with clonidine in pilot trials prompted a randomized controlled trial. In a double-blind, placebo-controlled, crossover trial of 77 men with prostate cancer treated with ADT, the efficacy of clonidine over placebo in reducing hot flashes was investigated.<sup>74</sup> Transdermal clonidine (equivalent to an oral dose of 0.1 mg/d) was administered for 4 weeks followed by 4 weeks of placebo or vice versa. In total, 50 patients completed the entire duration of the planned study. Hot flashes were reduced in 34% of patients treated with clonidine compared with 19% of patients on placebo; however, there was no statistically significant benefit for clonidine. The major reported toxicity was dry mouth, along with skin reaction and redness under the transdermal clonidine patch.

**Antidepressants.** Antidepressants have also been reported to be beneficial in the treatment of hot flashes. Specifically, selective serotonin reuptake inhibitors (SSRIs) have demonstrated efficacy in the treatment of hot flashes in some small series. As a

class of medications, these drugs are generally well tolerated and provide the additional benefit of treating depression. SSRIs used to treat hot flashes include venlafaxine (Effexor®; Wyeth; Madison, NJ), paroxetine (Paxil®; GlaxoSmithKline; Philadelphia, PA), and sertraline (Zoloft®; Pfizer; New York, NY).

A summary of 2 nonrandomized pilot studies using venlafaxine demonstrated efficacy in the treatment of hot flashes for men on ADT.<sup>75,76</sup> A total of 44 patients received 12.5 mg twice daily, and between 58% and 63% of patients reported at least a 50% decrease in hot flashes. A follow-up study in women with breast cancer evaluated higher doses of venlafaxine in managing hot flashes. A total of 191 patients were treated with placebo or venlafaxine at doses of 37.5 mg/d, 75 mg/d, or 150 mg/d.<sup>77</sup> Hot flashes decreased in all patient groups: by 27% for placebo, by 37% for venlafaxine 37.5 mg/d, and by 61% for venlafaxine 75 mg/d and 150 mg/d. Side effects of dry mouth, decreased appetite, nausea, and constipation were significantly increased at the higher doses of venlafaxine (75 mg/d and 150 mg/d).

Paroxetine was evaluated in 24 men with prostate cancer treated with ADT.<sup>75</sup> Patients received an initial dose of paroxetine at 12.5 mg/d that was subsequently increased to 37.5 mg/d. The median frequency of hot flashes decreased from 6.2 per day during baseline to 2.5 per day at the end of the study. Overall, paroxetine was well tolerated.

Sertraline, another SSRI, has been shown in case reports to reduce hot flashes in men on ADT.<sup>78</sup> Randomized, placebo-controlled studies in women with breast cancer demonstrated hot flash reduction with sertraline at 50 mg/d compared with placebo,<sup>79</sup> a reduction that is similar to those seen with other antidepres-

sants. A 50% reduction in the frequency of hot flashes after 6 weeks of therapy was seen in 36% of women taking sertraline (n = 25) compared with 27% of women taking placebo (P = .7). To date, there have been no randomized, controlled trials assessing the benefit of sertraline in men on ADT.

**Supplements and complementary medicine.** Dietary supplements and complementary medicine have also been reported to be of benefit for men experiencing hot flashes while on ADT. The list of potential agents includes soy and vitamin E. The success of soy may be due to its phytoestrogenic properties. In a randomized, controlled trial of 104 postmenopausal women, soy protein supplementation reduced hot flashes by 45%, as compared with a 30% reduction for placebo.<sup>80</sup> However, among 8 randomized clinical trials in women that evaluated soy for treating hot flashes, only 3 showed benefit.<sup>65</sup>

Vitamin E has demonstrated benefit. One randomized, controlled trial found hot flash reductions of up to 30% with vitamin E, as compared with 22% with placebo.<sup>81</sup> Acupuncture has also been reported as a means to control symptomatic hot flashes. One study of 7 castrated men with advanced prostate cancer who were experiencing hot flashes used this treatment approach.<sup>82</sup> Patients were treated with acupuncture twice weekly for 2 weeks, and then weekly for a total of 10 weeks. Of the 7 men in the study, 6 reported a 70% decrease in hot flashes.

**Selective estrogen receptor modulators.** The SERM toremifene is currently under investigation for the treatment of hot flashes in men. An ongoing phase III trial has already enrolled 1392 prostate cancer patients being treated with ADT. Hot flashes are a secondary endpoint for this trial. The rationale for the use of toremifene

in men on ADT includes the fact that toremifene acts as a weak estrogen in the pituitary. Hot flash incidence and severity (with a scale of mild, moderate, severe, and very severe) among these patients is being assessed at baseline and at 3, 6, 12, 18, and 24 months follow-up. Although the efficacy of SERMs remains under study, the mechanism of action may be in part due to the weak estrogenic effects that have been shown to be beneficial among castrated men, as noted previously. These data also suggest a different mechanism of action in men as compared with women; toremifene does not appear to improve hot flashes in women with breast cancer.

**Gynecomastia and Breast Tenderness**  
Gynecomastia, defined as benign proliferation of the glandular subareolar breast tissue, is an embarrassing and sometimes painful side effect experienced by men on ADT.<sup>57,60</sup> In some cases, gynecomastia may be disturbing enough to cause men to discontinue therapy.<sup>14</sup> As with many side effects of ADT, gynecomastia has not been systematically studied.

The incidence of gynecomastia varies with the type and duration of ADT.<sup>65,83</sup> For example, it is reported in 40% to 80% of men on estrogen therapy (eg, DES), 40% to 70% of men on antiandrogens (bicalutamide, flutamide, or nilutamide, including > 50% with high-dose bicalutamide [150 mg]), 25% of men on combined androgen blockade (LHRH with an antiandrogen), and 10% to 15% of men on LHRH alone or after orchiectomy.<sup>66</sup>

Gynecomastia is believed to be due to an increase in the ratio of estrogen-to-androgen activity often seen after treatment with ADT.<sup>57</sup> An increased testosterone level in men on antiandrogen monotherapy causes an increase in 17 $\beta$ -estradiol due to androgen aromatization. Gynecomastia

usually begins within 6 to 12 months of treatment and may initially be reversible.<sup>84</sup> Gynecomastia was reversible in the setting of short-term dosing of bicalutamide. For example, among those treated with high-dose bicalutamide, 64% of patients on the drug for less than 6 months achieved resolution of gynecomastia, but only 29% of patients on the drug for longer than 18 months had a similar outcome.<sup>85</sup> After 1 year, the hyalinization and fibrosis associated with gynecomastia are irreversible.

Assessing gynecomastia in patients is important but often not systematically performed. In clinical trials, glandular breast tissue (not fat) can be measured when the patient is supine and the diameter of the subareolar breast tissue is measured. Breast tenderness and breast pain can both be assessed using a 5-point scale rated as none (0), mild (1), moderate (2), severe (3), and extreme (4). There is currently no standard grading of gynecomastia, and therefore this scale or variations thereof allow urologists to begin to assess the magnitude of the condition as well as the impact of intervention.

**Prophylactic radiation therapy.** Gynecomastia may in part be prevented if prophylactic RT is initiated prior to therapy. In a review of 262 patients, prophylactic RT to the breast has been reported to have an 89% efficacy when administered before initiation of estrogen therapy.<sup>86</sup> In this study, efficacy was defined as minimal breast changes after therapy. In men on antiandrogen therapy, only 28% developed gynecomastia with prophylactic RT. However, RT may reverse breast tenderness but will not result in regression of gynecomastia once it is established.

Prophylactic RT is not routinely administered to patients planning to undergo either LHRH monotherapy or combined androgen blockade due to the relatively low incidence of gy-

necomastia. In contrast, RT is more commonly considered prior to initiation of antiandrogen monotherapy, particularly for high-dose antiandrogen therapy. In a study of men with prostate cancer treated with antiandrogen therapy, 28% developed gynecomastia with prophylactic RT compared with 71% who did not.<sup>87</sup>

**Breast reduction surgery.** Surgical correction of gynecomastia is an option for refractory gynecomastia.<sup>31</sup> Additionally, subareolar mastectomy can be performed at the time of the orchiectomy. Mastectomy may have similar results to prophylactic RT, but 15% of patients who undergo mastectomy will ultimately develop breast enlargement.<sup>87</sup> Surgery generally results in satisfactory cosmetic results in patients who fail RT or develop refractory gynecomastia, but medical management or prevention is preferable to any invasive procedures for this condition.

**Medical therapy.** Medical treatment for gynecomastia is directed at the underlying cause—an increase in estrogen. Effective treatment may result from either reducing estrogen levels or blocking estrogen-level activity.<sup>57,66</sup> This goal may be accomplished using SERMs, or aromatase inhibitors. These medications, however, may increase androgen secretion by blocking or reducing the negative feedback of estrogen on the hypothalamic-pituitary axis, so caution should be exercised in patients with prostate cancer until more safety and efficacy data are available.

The SERM tamoxifen has been evaluated in the treatment of gynecomastia. A randomized, placebo-controlled trial evaluated 114 men with prostate cancer with localized, locally advanced, or recurrent prostate cancer (Table 5).<sup>88</sup> Patients were randomized to 48 weeks of bicalutamide plus placebo, tamoxifen (20 mg/d), or anastrozole (1 mg/d). Gynecomastia

**Table 5**  
**Evaluation of Tamoxifen and Anastrozole in Prevention of Gynecomastia and Breast Pain Induced by Bicalutamide Monotherapy of Prostate Cancer**

	Placebo	Tamoxifen	Anastrozole
Gynecomastia	73%	10%	51%
Breast pain	39%	6%	27%
PSA decrease	97%	97%	83%
Adverse events	37%	35%	69%

PSA, prostate-specific antigen. Adapted with permission from Boccardo F et al.<sup>88</sup>

developed in 73% of patients in the bicalutamide-placebo group, 10% of patients in the bicalutamide-tamoxifen group, and 51% of patients in the bicalutamide-anastrozole group ( $P < .001$ ). Breast pain developed in 39% of patients in the bicalutamide-placebo group, 6% of patients in the bicalutamide-tamoxifen group, and 27% of patients in the bicalutamide-anastrozole group ( $P = .006$ ). Baseline PSA levels decreased in 97% of patients in both the placebo and tamoxifen groups and 83% of patients in the anastrozole group. Adverse events occurred in 37% of patients in the bicalutamide-placebo group, 35% of patients in the bicalutamide-tamoxifen group, and 69% of patients in the bicalutamide-anastrozole group.

In a similar study evaluating gynecomastia in men on therapy for prostate cancer, 107 subjects receiving bicalutamide were randomized to 3 months of bicalutamide plus placebo, tamoxifen (20 mg/d), or anastrozole (1 mg/d).<sup>89</sup> Gynecomastia, breast pain, or both occurred in 69% of patients in the bicalutamide-placebo group, 12% of patients in the bicalutamide-tamoxifen group, and 64% of patients in the bicalutamide-anastrozole group. The benefits did not persist

after withdrawal of tamoxifen in about 75% of patients, but two-thirds of patients responded to repeat treatment with tamoxifen. There was no difference in cancer control as assessed by PSA levels among the groups.

In a third study evaluating 102 men with prostate cancer receiving adjuvant bicalutamide, men were randomized to 24 weeks of bicalutamide alone, bicalutamide plus tamoxifen (10 mg/d), or prophylactic RT to the breast (12 Gy).<sup>90</sup> Gynecomastia and breast pain were significantly more common for patients receiving bicalutamide alone. Gynecomastia occurred in 67% of patients receiving bicalutamide alone, 8% of those receiving bicalutamide plus tamoxifen, and 34% of those receiving RT. Breast pain occurred in 58% of patients receiving bicalutamide alone, 7% of those receiving bicalutamide plus tamoxifen, and 30% of those receiving RT. There was no difference in cancer control as assessed by PSA relapse. Thus, tamoxifen was more effective than prophylactic RT for preventing bicalutamide-induced gynecomastia.

In summary, results from 3 randomized, controlled trials suggest that gynecomastia and breast pain

induced by bicalutamide can be prevented by tamoxifen.<sup>86-90</sup> Tamoxifen was also more beneficial than prophylactic RT, with no apparent increase in adverse events.<sup>90</sup> No large studies have been conducted to understand the safety of tamoxifen in men on ADT. The optimum dose of tamoxifen used in prophylaxis or treatment of gynecomastia or breast pain remains to be determined. Most studies used 20 mg/d, but doses of 10 mg/d to 40 mg/d have been used with similar results. The optimal duration of therapy is unknown.<sup>83</sup>

Currently, a phase III trial is being conducted to evaluate the efficacy of toremifene in 1392 prostate cancer patients on ADT. Gynecomastia and breast pain are secondary endpoints of this study. Toremifene may reduce breast enlargement and pain because it acts as an estrogen antagonist in breast tissue. Supine measurements for glandular tissue and assessment for gynecomastia pain and tenderness are part of the trial design. Incidence and severity of gynecomastia are being assessed at baseline and at 3, 6, 12, 18, and 24 months follow-up.

### Summary

Hot flashes remain a significant adverse side effect for men on ADT. Their hot flashes are often more severe and less prone to resolution than those experienced by women during menopause. Currently, MPA and the SSRIs appear to be the most efficacious and best tolerated treatments available for men on ADT with symptomatic hot flashes. Estrogens are beneficial, but concerns over side effects have tempered enthusiasm for their use. Complementary and alternative therapies are also attractive, but their efficacy is still largely unproven. For all treatment options, well-organized, double-blind, placebo-controlled trials are needed in men on ADT to determine the true benefit.

Gynecomastia is a distressing and often embarrassing side effect experienced by men with prostate cancer treated with ADT. Incidence varies by type and duration of therapy. Prevention includes therapy directed at reducing the effects of excess estrogen by reducing estrogen levels or blocking estrogen level activity as well as prophylactic RT. Prophylactic RT has been among the most common therapies, often recommended before high-dose antiandrogens. Bicalutamide-induced gynecomastia can be prevented by or treated with SERMs. Once gynecomastia is established, treatments include medical therapy or surgery, with a minor role for RT in reducing breast pain. The long-term effects of medical therapies and their impact on cancer control require further study.

Cardiovascular Disease

The most common cause of death in the United States is cardiovascular disease. Risk factors are listed in Table 6.<sup>91</sup> With respect to age and sex, the risk is increased in men who are 45 years or older. A significant family history includes premature coronary

heart disease, defined as a myocardial infarction or sudden death in a first-degree relative before age 55 in men or age 65 in women. Hypertension is a risk when blood pressure is greater than 140/90 mm Hg or when the patient is on medication for hypertension. The cholesterol value that imparts the greatest risk is a high-density lipoprotein (HDL) level less than 40 mg/dL. Men of Mexican American, native American, native Hawaiian, and some Asian American racial groups are at increased risk of cardiovascular disease.

ADT has been shown to result in a multitude of metabolic and physiologic changes when compared with pretreatment measurements. Many of these changes, listed in Table 7, can increase an individual's pre-existing cardiovascular risk. These factors are discussed in more detail below.

ADT significantly alters lipid profiles in men with prostate cancer. Most prospective studies have reported that GnRH agonists increase serum total cholesterol, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, and triglycerides.<sup>92-93</sup> In a prospective, 12-month study of 40 men with non-metastatic prostate cancer, for example,

GnRH agonists increased serum total cholesterol by 9.0%, LDL cholesterol by 7.3%, HDL cholesterol by 11.3%, and triglycerides by 26.5%.<sup>93</sup> Most, but not all, of the long-term treatment-related changes in serum lipids are apparent after as little as 3 months of treatment.<sup>94</sup>

Hypogonadal men may be at increased risk of developing diabetes,<sup>95,96</sup> which can be treated with testosterone replacement.<sup>97</sup> It is not surprising then that ADT can also induce a state of insulin resistance, with resulting glucose intolerance or frank diabetes. Insulin resistance due to ADT occurs independently of body mass index or age factors.<sup>98</sup> Compared with baseline values before treatment with ADT, fasting insulin levels<sup>94,99,100</sup> are elevated, even though fasting glucose levels may not be significantly changed.<sup>94,99,100</sup> Interestingly, in the 2 studies in which it was measured, the hemoglobin A<sub>1c</sub> was increased, demonstrating an overall increase in mean serum glucose levels over the prior 8 to 12 weeks.

ADT can also lead to weight gain that causes or compounds obesity, another risk factor for cardiovascular disease. Although the magnitude of weight gain during treatment is in the range of 2% to 3% for the study populations overall,<sup>93,101,102</sup> individual patients can gain up to 10% to 20% of their baseline weight.<sup>103</sup> Specifically, lean body mass falls while total body fat rises when measured at 12 or 52 weeks after initiation of ADT.<sup>99,102,104</sup>

Pulse wave analysis studies done before and 3 months after the start of ADT have demonstrated a decrease in systemic arterial compliance or an increase in central arterial stiffness,<sup>99,100</sup> a known risk factor for cardiovascular disease. Although these studies did not find a significant change in peripheral blood pressure readings after 3 months, there are anecdotal reports of exacerbation of pre-existing

Table 6 Risk Factors for Cardiovascular Disease
Hypertension
High cholesterol
Smoking
Physical inactivity
Obesity
Diabetes
Family history
Sex
Age
Race
Adapted with permission from the American Heart Association. <sup>91</sup>

Table 7 ADT Effects on Cardiovascular Risk Factors
Alteration in lipids <sup>93</sup>
Increase in body weight <sup>93</sup>
Increase in body mass index <sup>93</sup>
Increase in body fat, decrease in lean body mass <sup>93,102</sup>
Increase in fasting insulin levels <sup>94</sup>
Increase in hemoglobin A <sub>1c</sub> <sup>94</sup>
Decrease in arterial compliance <sup>100</sup>
Prolongation of QT interval <sup>105</sup>
ADT, androgen deprivation therapy.

**Table 8**  
Increased Risks in Men Treated With ADT in the SEER Medicare Database\*

	Adjusted Hazard Ratio	P Value
Incident diabetes	1.44	.001
Coronary heart disease	1.16	.001
Myocardial infarction	1.11	.03
Sudden cardiac death	1.16	.004

\*As compared with men who did not receive ADT. SEER, Surveillance, Epidemiology, and End Results. Adapted with permission from Keating NL et al.<sup>105</sup>

hypertension or a new diagnosis of hypertension after starting ADT.<sup>103</sup>

That ADT can result in both diabetes and cardiovascular disease was shown in a large observational study of 73,196 men with localized prostate cancer in the Surveillance, Epidemiology, and End Results (SEER) Medicare database.<sup>105</sup> This study demonstrated that those treated with ADT in the form of a GnRH agonist had an increased risk of the development of diabetes and coronary heart disease, including myocardial infarction and sudden death, as compared with those who did not receive ADT (Table 8).

#### Recommendations

Because ADT has the potential to adversely affect cardiovascular risk factors, the risks and benefits of therapy for a given patient must be carefully considered. To start, the presence of cardiovascular risk factors for an individual patient should be reviewed. If ADT is to be administered, patients should be educated about all of the possible side effects, with emphasis on the potential impact of ADT on overall health. Patients should be advised to take proactive measures to avoid or minimize toxicities. Referral to a nutritionist is advised so patients can be counseled on healthy dietary

habits and strategies for minimizing weight gain. Consultation with a physical therapist or a licensed physical trainer should teach patients how to engage in a combination of aerobic and resistance exercises that will be beneficial in terms of improving cardiovascular health, maintaining muscle mass, and decreasing weight gain. Exercise may also offset many other adverse effects due to ADT, including loss of BMD, hot flashes, fatigue, and depression.<sup>106</sup>

In the office, minimum baseline testing should include weight measurement, blood pressure reading, and fasting lipid panel and serum glucose tests. These assessments should probably be repeated 3 months after initiation of ADT and at least every 6 to 12 months thereafter during administration of ADT. The clinician should be alert for new or worsening hypertension, diabetes, hyperlipidemia, or symptoms of cardiac ischemia. It is important to coordinate with other caregivers when changes occur or when the patient already has underlying problems that might be exacerbated by ADT.

#### Summary

Although some of the risk factors for cardiovascular disease—such as sex,

**Table 9**  
Modifiable Risk Factors for Cardiovascular Disease

Smoking
Dyslipidemia
Hypertension
Diabetes
Abdominal obesity
Psychosocial factors
Inadequate daily consumption of fruits and vegetables
Immoderate alcohol consumption
Insufficient regular physical activity

Data from the American Heart Association.<sup>91</sup>

age, and race—cannot be changed, patients who are going to be treated with ADT need to be educated about the many risk factors that can be modified by lifestyle changes.<sup>107</sup> Physicians must be alert for treatable risk factors (Table 9).<sup>108</sup> Although no prospective trials have addressed the effects of interventions to minimize cardiovascular risks due to ADT, there is no reason to believe that the usual interventions for specific risk factors would not be beneficial. If patients who have longer life expectancies are to be treated with ADT, it is incumbent on health care providers to consider strategies that minimize morbidity and mortality due to cardiovascular disease.

#### Conclusion

It is critical for urologists to identify and treat the adverse sequelae associated with ADT.

Men receiving ADT should undergo screening, prevention, and treatment of bone loss. The most common bothersome side effects of ADT—hot flashes, gynecomastia, and breast tenderness—have several treatment options. ADT can adversely affect cardiovascular risk factors. Urologists

should be alert for new or worsening signs or symptoms. ■

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## Main Points

- The impact of androgen deprivation therapy (ADT) on estrogens and androgens that modulate bone remodeling often results in rapid and significant loss of bone mineral density (BMD).
- Early diagnosis of bone loss and prompt initiation of preventive and pharmacologic measures to delay or prevent decreased BMD are essential in men with advanced prostate cancer who are initiating ADT.
- Hot flashes remain a significant adverse side effect for men on ADT. Medroxyprogesterone acetate and the selective serotonin reuptake inhibitors appear to be the most efficacious and best tolerated treatments.
- Gynecomastia is a distressing and often embarrassing side effect experienced by men with prostate cancer treated with ADT. Prophylactic radiation therapy has been among the most common therapies, often recommended before high-dose antiandrogens.
- Although some of the risk factors for cardiovascular disease—such as sex, age, and race—cannot be changed, patients who are going to be treated with ADT should be educated about the many risk factors that can be modified by lifestyle changes.

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